576. *Syntheses with 4-Alkylideneoxazolones. Part I. The Condensation of Aliphatic Aldehydes with Hippuric Acid.*

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The conditions under which aliphatic aldehydes may be used in the Erlenmeyer azlactone synthesis have been investigated, and much improved yields have been obtained with lead acetate as the catalyst.

The Erlenmeyer azlactone synthesis has proved a useful means of obtaining many α-amino-acids and substituted pyruvic acids. The literature on the subject to 1945 has been reviewed by Carter ("Organic Reactions," 1946, Vol. III, 198), who also indicates the variety of derivatives obtainable. However, the synthesis has so far been confined to the condensation of *N*-acylated glycines with aromatic aldehydes or αβ-unsaturated aldehydes, with three exceptions mentioned below; the present communication describes its extension to simple aliphatic aldehydes.

The only catalyst used in reported condensations of saturated aliphatic aldehydes with hippuric acid is sodium acetate in acetic anhydride. Using a nine-fold excess of acetaldehyde, Carter, Handler, and Melville (*J. Biol. Chem.*, 1939, **129**, 359) obtained a 15—20% yield of 2-phenyl-4-ethylideneoxazol-5-one. With only slightly different conditions, Corse, Kleiderer, and Soper (*J. Amer. Chem. Soc.*, 1948, **70**, 438) obtained about 40% of the 4-*n*-propylidene derivative. Erlenmeyer and Kunlin (*Annalen*, 1901, **316**, 145) used only one molecular proportion of *iso*butyraldehyde at 100°; they stated that the yield of 2-phenyl-4-*iso*butylideneoxazol-5-one was poor, but gave no figures. In our hands this method gave about 8% yield. Evans and Walker (*J.*, 1947, 1571) were unable to condense *p*-methoxyphenylacetaldehyde with hippuric acid.

In our first exploratory experiments two mols. of acetaldehyde were used; it was later found possible to reduce this further to 1·1 mols. As the American authors had stressed the deleterious effect of temperatures above 60°, our early investigations were carried out at laboratory temperature with mechanical shaking, usually for 48 hours. Many different catalysts were tried. Johnson ("Organic Reactions," 1942, Vol. I, 237) has discussed the various metallic acetates that have been used as catalysts in the related Perkin reaction, and in general it has been found that the yields increase with the electropositive character of the metal. We have found the reverse to be true in the synthesis of alkylideneoxazolones when using the alkali metal acetates as catalysts, the acetates of the more strongly electropositive metals giving rise to red gummy by-products. Thus with potassium acetate the reaction was very exothermic, giving a gummy product from which only a small yield of azlactone was isolated; with lithium acetate the reaction was not vigorous and no gum was formed, but the yield of pure azlactone was now 30%; sodium acetate was intermediate in effect.

The salts of metals of other groups were also investigated, cupric and mercuric acetates being ineffective, whilst thallous, calcium, and barium acetates gave low yields. When, however, anhydrous lead acetate, its trihydrate, or a commercial basic lead acetate was used, the yield rose to 50—60%.

Yields of 0—15% were obtained when various nitrogenous bases, such as ammonium acetate, triethylamine, and acetamide, also piperidine, morpholine, and their *N*-acetyl compounds, were used as catalysts.

It was found that temperature had a profound influence on the rate of reaction. Thus in most cases reaction was substantially complete after 36 hours at 20—23°. Below about 18° there was no reaction when lead acetate was used as catalyst; on the other hand, approximately the same yields were obtained in 10—20 minutes at 100° as after 36—48 hours at 20°. Although this involves the use of pressure vessels for acetaldehyde and propionaldehyde it appears to be the most convenient for *n*- and *iso*-butyraldehyde, no simple aldehydes beyond these having yet been examined.

Attempts to use aceturic acid or acetals (cf. Yuan and Li, *J. Chinese Chem. Soc.*, 1937, **5**, 214) were unsuccessful, and the yield decreased when the amount of catalyst was reduced below one equivalent. The replacement of sodium acetate by lead acetate in the condensation of benzaldehyde with hippuric acid did not result in an improved yield.

EXPERIMENTAL.

Effect of Various Catalysts in the Condensation of Acetaldehyde with Hippuric Acid.—Acetic anhydride (16 ml., 0·15 mol.), hippuric acid (8·95 g., 0·05 mol.), and the catalyst (0·05 equiv.) were added successively to acetaldehyde (4·4 g., 0·1 mol.) in a glass-stoppered tube, and the mixture was shaken at laboratory temperature for 15 hours. During this period the solid generally dissolved, and long needles began to separate. Although reaction was usually almost complete at this stage, the mixture was kept for a further 33 hours, with occasional shaking, and then poured into water (150 ml.). After all the acetic anhydride had hydrolysed (*ca.* 1 hour) the crude yellow product was filtered off, washed with water, and dried at 50°. It was recrystallised from 50% aqueous ethanol, forming nearly colourless needles. On a larger scale this solvent caused some loss by hydrolysis; purification was effected by dissolving the crude product in four times its weight of hot acetone, filtering, and carefully adding about twice its weight of cold water. With anhydrous or basic lead acetate the yield of product, m. p. 91—92°, was 58%; with the trihydrate 50%, m. p. 89—90°. The pure oxazolone melts at 95—96° and distils as a colourless oil at 110—112°/0·1 mm.

Effect of Temperature.—The same quantities of reactants were heated in a steam-jacketed sealed tube for 10 minutes, and a clear yellow solution was obtained. Lithium and lead acetates as catalysts gave yields of 29% and 53%, respectively.

Condensation of Other Aldehydes.—The aldehyde (0·06 mol.), acetic anhydride (16 ml., 0·15 mol.), hippuric acid (8·95 g., 0·05 mol.), and lead acetate (8·13 g., 0·05 equiv.) were shaken at 20—23° for 15 hours, left for 33 hours, and then treated as above. The yields obtained are :

Aldehyde.	Yield, %.	M. p.	M. p. of pure compound.
Acetaldehyde	39	89—90°	95—96°
Propionaldehyde	45	83—84	84
n-Butyraldehyde	7	57	57
*iso*Butyraldehyde	31	84—83	87

[Corse, Kleiderer, and Soper (*loc. cit.*) give the m. p. of the 4-propylidene derivative as 81—83°.]

*2-Phenyl-4-*n*-butylideneoxazol-5-one.*—A yield of only 7% was obtained with the above conditions. A mixture of *n*-butyraldehyde (17·3 g., 0·24 mol.), acetic anhydride (64 ml., 0·6 mol.), hippuric acid (35·8 g., 0·2 mol.), and lead acetate (32·5 g., 0·1 mol.) was heated under reflux for 20 minutes, and the clear orange solution was then poured into water (600 ml.). After some hours the gummy product was extracted with boiling light petroleum (b. p. 40—60°; 5 × 80 ml., which extract on evaporation of the solvent gave a yellow solid (9·3 g.; 22% yield), m. p. 52—54°. Recrystallisation from methanol gave colourless flattened needles, m. p. 57°, of the *oxazolone* (Found : C, 72·7; H, 6·5; N, 6·4. $C_{13}H_{13}O_2N$ requires C, 72·5; H, 6·1; N, 6·5%).

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